## REMARKS

Since a RCE is being filed herewith, it is requested that this amendment be entered and considered at this time.

## I. Claim Amendments – Reference to Disclosure

As explained in depth below, while Applicants respectfully traverse the rejections in the June 15, 2004 Final Rejection, in order to advance the prosecution of this application, independent Claims 1, 16, 22, 29, 46 and 47 have been amended to bring them into better conformance with the disclosure in the specification. In particular, these claims are now more explicitly directed to (a) radiosensitizer pharmaceutical compositions or medicaments, wherein (b) such compositions or medicaments are activated using applied ionizing radiation having an energy of greater than approximately 1 KeV, (c) the claimed halogenated xanthenes are further defined to consist of sodium or potassium salts formulated in a pharmaceutical delivery vehicle, and (d) provided that the halogenated xanthene active ingredient of such compositions or medicaments does not contain a radioisotope. Each of these features is clearly supported by the application as filed as explained below.

Examples in support of such claimed pharmaceutical compositions or medicaments are found throughout the specification. For instance, Applicants' Field of the Invention describes the radiosensitizers of the claims of the present application in the following terms:

> "The present invention is directed to certain radiodense medicaments and methods for treatment of human or animal tissue using such medicaments in combination with radiation therapy, wherein these radiodense medicaments serve as *radiosensitizers* in high energy phototherapy. The inventors of the present invention have found that such medicaments are useful for *treatment of a variety of [disease]*

> *conditions*.... These medicaments are in various formulations that may include liquid, semisolid, solid or aerosol delivery vehicles, and are suitable for *intracorporeal administration* via various conventional modes and routes.... Irradiation of tissues containing such medicaments with ionizing radiation produces a desirable therapeutic response...." (p. 1, lines 11- 25, emphasis added)

Accordingly, this passage clearly defines the claimed radiosensitizer medicaments as intracorporeal pharmaceutical agents that potentiate the therapeutic effects of applied ionizing radiation.

In the Summary of the Present Invention, Applicants further define this claimed subject matter, as indicated by the following passage from the application:

> "The present invention is directed to new *intracorporeal radiodense medicaments* ... for treatment of human or animal tissue, wherein a primary active component of such medicaments is a halogenated xanthene or a halogenated xanthene derivative, and more preferably Rose Bengal or a functional derivative of Rose Bengal. The halogenated xanthenes constitute a family of potent radiosensitizers that are *activated upon irradiation* of the treatment site with ionizing radiation, such as x-rays. Such medicaments are suitable for intracorporeal administration, and are thus *intracorporeal medicaments*. Such medicaments can also be called *pharmaceutical compositions* or agents." (p. 5, line 19 - p. 6, line 3, emphasis added)

As this passage indicates, the subject matter and claims of the present application are directed to therapeutic agents (i.e., intracorporeal radiosensitizer medicaments or pharmaceutical compositions) that become therapeutically active upon irradiation of the treatment site with applied ionizing radiation. The type of applied ionizing radiation is further specified by, among other passages, the following from the application:

> "The halogen content of the halogenated xanthenes makes this class of agent highly efficient absorbers of x-rays or other *ionizing radiation* of energy *greater than approximately 1 keV* and less than approximately 1000 MeV, and thus suitable as radiodense components in various radiosensitizer medicaments used in conjunction with such radiation in high energy phototherapy." (p. 9, lines 10-14, emphasis added)

Hence, the claimed applied ionizing radiation of the present application is radiation having an energy

greater than approximately 1 keV.

Together, these passages illustrate that Applicants' invention as claimed comprises therapeutic medicaments for radiosensitization that contain a halogenated xanthene, where such medicaments become active upon application of ionizing radiation to the treatment site. These agents are non-hazardous by themselves, as further illustrated by the following passage from the application:

> "In general, the halogenated xanthenes are characterized by a large radiation absorbance cross-section, *low dark cytotoxicity* (toxicity to cells or tissues in the absence of radiation), high light cytotoxicity (toxicity to cells or tissues upon irradiation)..." (p. 9, .line 23 - p. 10, line 3, emphasis added)

This passage further describes the subject matter of the present application and claims as non-radioactive forms of the halogenated xanthenes, since the radioactive forms (such as those described in Serafini) are inherently toxic to cells or tissues in the absence of applied radiation.

Examples in support of the amendments to the claims to recite sodium or potassium salts of the halogenated xanthenes are found, for instance, in Table 1 of the present application, which illustrates that groups $R^1$ and/or $R^2$ of the halogenated xanthenes (see Figure 1b for the structural designation of these groups) may be, for example, sodium (Na) or potassium (K). This particular identity of the claimed halogenated xanthenes is further illustrated by Figure 1a, which shows Rose Bengal in its dibasic form (i.e., as a disodium salt).

Examples in support of the amendments to the claims to recite formulation of the claimed halogenated xanthenes in a pharmaceutical delivery vehicle are found, for instance, in the following passage from the application:

> "Because the halogenated xanthenes and their derivatives are, in general, fine solid powders in their pure form, it is preferred that, for proper delivery to desired

> tissues, such agents be *formulated in appropriate delivery vehicles*. Approaches to such formulation will be generally known to those of ordinary skill in the art. Specifically, such formulations are preferred so as to facilitate agent delivery into the body and subsequent contact with, and delivery to, desired tissues to be treated.... Such suitable forms include medicaments formulated in a *liquid, semisolid, solid or aerosol delivery vehicle*, including aqueous suspensions, non-aqueous suspensions, solutions, creams, ointments, gels, syrups, micro-droplet sprays, suppositories, tablets and capsules." (p. 15, lines 13-23, emphasis added)

As indicated by the cited passage, pharmaceutical delivery vehicles are generally known to those of skill in the art, and include liquids, semisolids, solids and aerosols.

Applicants have amended independent Claims 1, 16, 22, 29, 46 and 47 to better reflect these teachings, in particular with regard to the specific aspects of the applied ionizing radiation and identity of the claimed halogenated xanthenes. As explained *supra*, such amendments have not added any new matter. Moreover, Applicants believe that such amendments clarify the claimed radiosensitizer pharmaceutical compositions or medicaments and methods for use of such pharmaceutical compositions or medicaments of the present application.

Accordingly, for at least the above-stated reasons, it is respectfully submitted that the amendments to the claims are supported by the application as filed. Therefore, it is requested that they be entered.

Applicants will now address each of the Examiner's rejections and comments in the order in which they appear in the Final Rejection.

## II. Claim Rejections – 35 USC §112

In the Final Rejection, the Examiner rejects Claims 16-28 under 35 U.S.C. 112, second paragraph, as being indefinite. In order to advance the prosecution of this application, independent

Claims 16 and 22 have been amended to correct certain alleged informalities in claim language. These amendments should overcome the Examiner's objections. Therefore, it is respectfully requested that rejection of these claims, and all claims dependent thereupon, under §112 be withdrawn.

## III. Claim Rejections – 35 USC §102 (Serafini)

The Examiner also rejects Claims 1, 3, 5, 8-12, 15-18, 20, 29, 31, 33, 36-39, 46-48 and 50 under 35 U.S.C. §102(b) as being anticipated by Serafini. This rejection is respectfully traversed for at least the following reasons. As explained in more depth below, Serafini does not disclose or suggest the invention of the amended claims of the present application.

For example, Serafini does not disclose or suggest a sodium or potassium salt of a halogenated xanthene as recited in the claims. Instead, Serafini dissolves the acid form of Rose Bengal (i.e., not a salt form) in pH 7.2. phosphate buffer (see e.g. page 630, col. 1, second paragraph in Serafini).

Additionally, Serafini does not describe the claimed pharmaceutical compositions, medicaments, and uses. Regarding Serafini, the Examiner contends on p. 6 of the current Final Rejection that "Serafini teaches [a medicament] for treating diseased tissue as a radiopharmaceutical agent." Applicants respectfully disagree with this assertion, for the reasons of record detailed in Amendment A filed on April 22, 2003.

In contrast to the Examiner's contention, Serafini teaches specific *diagnostic uses* of ceratin *radioactive forms* of Rose Bengal. Amended independent Claims 1, 16, 22, 29, 46 and 47, of the presently application, however, require *non-radioactive forms* of Rose Bengal (and other halogenated

xanthenes) for *therapeutic treatment* (i.e., the claimed materials are radiosensitizers). Serafini fails to suggest any non-radioactive forms of Rose Bengal or Rose Bengal for therapeutic treatment. More specifically, the radioactive forms of Rose Bengal disclosed in Serafini are structurally distinct from the non-radioactive forms of the claimed invention. Hence, Serafini does note anticipate nor render obvious the presently claimed invention.

Further, Serafini uses 2 mL of RB solution, delivered intravenously, at a concentration of 1.8 to 2.2 mg RB/mL (i.e., 0.18 to 0.22% RB). This dosage (ca. 4 mg RB / 70 kg body weight, or 0.06 mg RB/kg) is insufficient for treatment with ionizing radiation, and in fact, may be insufficient by a factor of almost 1000-fold. For the agent disclosed in Serafini to function as a radiosensitizer the concentration would need to be much higher or the administered volume much greater. In either case, the dose of radiation delivered to the subject would likely kill the subject in short order, as Serafini uses a highly radioactive form of Rose Bengal. Thus, the composition disclosed in Serafini cannot be used as a radiosensitizer, as recited in the claims of the present application.

For at least the above-stated reasons, Serafini fails to disclose or suggest the pharmaceutical compositions, medicaments or uses of amended independent Claims 1, 16, 29, 46 and 47 of the present application. Accordingly, these independent claims and those claims dependent thereon are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

## IV. Claim Rejections – 35 USC §102 (Neckers)

The Examiner also rejects Claims 1, 3, 5, 8-10, 12, 16, 18, 20, 29, 31, 33, 36-39, 46-48 and 50 under 35 U.S.C. §102(b) as being anticipated by Neckers. This rejection is also respectfully traversed for at least the following reasons. As explained in more depth below, Neckers does not

disclose or suggest the invention of the amended claims of the present application.

In particular, Neckers does not describe or suggest the claimed pharmaceutical compositions, medicaments, and uses. Regarding Neckers, the Examiner contends on p. 7 of the current Final Rejection that "Neckers teaches a medicament or pharmaceutical composition consisting of a halogenated xanthene ... [and] that Rose Bengal has selective concentration in selected tissue, i.e. tumor...." Applicants have carefully studied Neckers and find no hint of such teachings in the reference (no cite is provided in the Final Rejection as to where this alleged teaching is shown in Neckers). Instead, this reference is limited to discussion of physical properties such as the spectral properties, photochemical reactivity and photophysical parameters of Rose Bengal, not biological or pharmaceutical properties. These spectral properties, photochemical reactivity and photophysical parameters (i.e., physical properties) do not pertain to, nor hint at, the special biological properties (i.e., concentration in tumor tissue and potential for increasing the effects of applied ionizing radiation in such tissue) discovered, disclosed and claimed by Applicants in the present application.

If the Examiner disagrees, then Applicants respectfully request that the Examiner indicate the specific passages in Neckers that disclose concentration of a halogenated xanthene in tumor tissue or therapeutic interaction of a halogenated xanthene with applied ionizing radiation having an energy of greater than approximately 1 KeV.

Instead, Neckers discusses the molecule Rose Bengal and certain physical properties or the molecule (particularly as these pertain to visible radiation). Neckers does not disclose or discuss any interaction with ionizing radiation, nor its pharmaceutical use as an active ingredient in a radiosensitizer pharmaceutical composition. In fact, Neckers does not disclose or suggest any radiosensitizer pharmaceutical compositions. Pharmaceutical compositions are carefully defined

compositions consisting of one or more *active ingredient* in an appropriate pharmaceutical vehicle, and must encompass specific indications and usage parameters (such as indicated for "treatment diseased tissue" and for usage as a "radiosensitizer" with applied ionizing radiation). Each of the independent claims of the present application specifically recite such features. In contrast, the disclosure in Neckers fails to provide any disclosure of these features. The chemical Rose Bengal and the claimed pharmaceutical compositions or medicaments containing Rose Bengal of the present application are not the same physical entities, and accordingly, Neckers cannot anticipate nor render obvious the presently claimed invention.[1]

For at least the above-stated reasons, Neckers fails to disclose or suggest the pharmaceutical compositions, medicaments or uses of amended independent Claims 1, 16, 29, 46 and 47 of the present application. Accordingly, these independent claims and those claims dependent thereon are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

## V. Claim Rejections – 35 USC §102 (Fondren)

In the Final Rejection, the Examiner also rejects Claims 1, 3-5, 16, 18, 19, 29, 31-33, 46, 47 and 50 under 35 U.S.C. §102(b) as being anticipated by Fondren. This rejection is also respectfully traversed for at least the following reasons. As explained in more depth below, Fondren does not disclose or suggest the invention of the amended claims of the present application.

For example, Fondren does not disclose or suggest a sodium or potassium salt of a halogenated xanthene as recited in the claims.

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[1] It is noted that most integrated circuits are fabricated from silicon, which is accordingly a necessary component. Nonetheless, knowledge of silicon and some of its general physical properties does not render all integrated circuits obvious.

Further, Fondren does not describe or suggest the claimed pharmaceutical compositions, medicaments, and uses, nor does the reference in any way disclose or suggest the unexpected benefit achieved by the claimed compositions, medicaments and uses of the present application. Instead, Fondren describes pesticidal uses of simple aqueous solutions of certain halogenated xanthenes. Such uses and compositions do not include a pharmaceutical vehicle nor therapeutic treatment, as required in Applicants' amended independent claims.

Further, regarding the rejection based on Fondren, the Examiner contends on p. 10 of the current Final Rejection that "it is a general rule that merely discovering and claiming a new benefit (other than toxicity) of an old product cannot render the product again patentable." However, the claimed pharmaceutical compositions, medicaments, and uses are not an old product, as there are no radiosensitizer pharmaceutical compositions, radiosensitizer medicaments, or existing or former uses for a radiosensitizer pharmaceutical product consisting of halogenated xanthene.

Moreover, Applicants have discovered, and describe in the specification of the present application, new toxic properties of the halogenated xanthenes. Previously, in the absence of applied radiation, the halogenated xanthenes were believed to be essentially non-toxic.[2] The present application, however, shows that upon application of ionizing radiation, the halogenated xanthenes exhibit unanticipated toxicity to diseased tissue. Accordingly, Applicants have written the claims of the present application so that they recite a halogenated xanthene and ionizing radiation. Fondren fails to anticipate or suggest the novel toxicity properties of the claimed invention while also failing to describe or suggest the claimed pharmaceutical compositions, medicaments and uses of the

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[2] For example, in Serafini, the diagnostic agents are not believed to poison the patient. Fondren notes that Rose Bengal has been used as a food dye, which presumably is non-toxic.

present application.[3]

For at least the above-stated reasons, Fondren fails to disclose or suggest the pharmaceutical compositions, medicaments or uses of amended independent Claims 1, 16, 29, 46 and 47 of the present application. Accordingly, these independent claims and those claims dependent thereon are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

## VI. Claim Rejections – 35 USC §103 (Neckers and Norman)

The Examiner also rejects Claim 14 under 35 U.S.C. 103(a) as being unpatentable over Neckers in view of Norman et al. This rejection is respectfully traversed.

More specifically, in the Final Rejection, the Examiner combines the teachings of Neckers and Norman to arrive at this rejection. Such a combination is improper for at least the following reasons.

### A. Neckers does not teach any properties of the halogenated xanthenes with respect to ionizing radiation.

In the Office Action of September 23, 2003, the Examiner acknowledged that Neckers fails to disclose any properties of the halogenated xanthenes with respect to ionizing radiation. Nonetheless, in the present Final Rejection, the Examiner argues that Neckers has relevance because it "teaches and describes that halogenated xanthenes such as Rose Bengal have usefulness as contrast agent because of its properties: 1) as a photodynamic sensitizer, and 2) its capacity to be activated as an imaging agent, i.e. shows fluorescence." (Final Rejection, p. 9) However, since Neckers does

[3] For example, Fondren does not describe or suggest a composition suitable for intracorporeal use as a pharmaceutical composition, which must be sterile and pyrogen free, requirements which are known to those of skill in the art to be required for such use.

not teach any properties of the halogenated xanthenes with regard to ionizing radiation having an energy of greater than 1 keV, as previously acknowledged by the Examiner and required by the amended claims of the present application, this reference cannot be combined with the teachings of Norman[4] to arrive at the presently claimed invention.

For instance, Neckers' observation that Rose Bengal has properties as a photodynamic sensitizer has no relevance nor predictive value regarding possible interaction of the molecule with ionizing radiation having an energy of greater than 1 keV. As Applicants discussed in Amendment B in response to the September 23, 2003 Office Action, the highest energy noted in Neckers is 380 nm (Neckers p. 20, last line; a wavelength of 380 nm is equal to an energy of 0.003 keV). Photosensitizer properties at energies less than or equal to 0.003 keV have no relevance or predictive value regarding potential radiosensitizer properties at energies of greater than 1 keV. Hence, the photodynamic sensitizer properties of Rose Bengal, as noted in Neckers, is not relevant and cannot anticipate or predict the composition of the claimed invention or the radiosensitizer properties discovered by Applicants with regard to the claimed invention.

Similarly, Neckers' observation that Rose Bengal exhibits fluorescence properties upon illumination with light at energies less than or equal to 0.003 keV has no relevance or predictive value regarding potential interaction of the molecule with radiation at energies of greater than 1 keV (i.e., as a contrast medium for such energies greater than 1 keV). The optical fluorescence properties of a given material arise from features that are completely unrelated to features that determine

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[4] As described in detail in Applicants' response to the Office Action of September 23, 2003 (i.e. Amendment B), Norman does not describe features of halogenated materials but rather of materials containing the element gadolinium, which are in no way related to halogens or the halogenated xanthenes.

absorption of ionizing radiation having energies greater than 1 keV. Thus, knowledge that Rose Bengal exhibits fluorescence upon illumination with light has no relevance or predictive value regarding potential use as an imaging agent (much less for treatment purposes) using ionizing radiation at energies of greater than 1 keV. Hence, the fluorescence properties of Rose Bengal is not relevant and cannot anticipate nor predict the claimed invention or the radiosensitizer properties discovered by Applicants with regard to the claimed invention.

Accordingly, for at least the aforementioned reasons, Neckers has no relevance with respect to the properties of the halogenated xanthenes as delimited in Claim 14.

B. The gadolinium-based contrast media of Norman are not related to the halogenated xanthenes

Further, the Examiner states that Norman teaches about certain properties of certain contrast media, such as gadolinium contrast media. The Examiner also contends that these are related to the halogenated xanthenes, which the Examiner alleges to be "known for [their] use as a contrast agent." (p. 8, Final Rejection) However, contrary to these statements by the Examiner, the halogenated xanthenes, prior to the work of the present inventors as described herein and in the present application, were not known to have utility for contrast with ionizing radiation (i.e., as a contrast agent or contrast media). Accordingly, one skilled in the art upon reading Norman would not be led to apply knowledge of x-ray contrast agents to the halogenated xanthenes of Neckers.[5] Norman's teachings that the iodine in iodinated contrast media can yield a progressive dose enhancement is

[5] As described *supra*, Neckers disclosure is limited solely to interaction of visible light with the halogenated xanthenes. Visible light and the ionizing radiation of Norman are the subject of completely different fields of science. Neckers does not hint at possible interaction of the halogenated xanthenes with ionizing radiation nor at any possible use as a contrast agent with such radiation.

insufficient enablement to lead the skilled practitioner to conclude (1) that the halogenated xanthenes could be used as contrast media and then (2) that such newly discovered contrast media could be used as a radiosensitizer. As a result, the required teaching or motivation to combine these references is missing. Hence, the combination of them is improper.

C. Rose Bengal was not known to have usefulness as a contrast agent for ionizing radiation at the time of the invention; thus, Norman does not lead to application of general knowledge of contrast media to the halogenated xanthenes.

The possible use of any halogenated xanthene as a contrast agent for imaging with applied ionizing radiation (i.e., use as a contrast medium) was unknown to the public when the present invention was filed. United States Patent 6,493,570 was granted to two of the listed inventors of the present invention (i.e., Dees and Scott) for being first to conceive of the novel use of the halogenated xanthenes as contrast agents for methods for imaging with applied ionizing radiation. Prior to these inventors' conception, such use is believed to have been unknown to others skilled in the art. Accordingly, since possible use of Rose Bengal as contrast media was unknown, one skilled in the art reading Norman would not be led to apply Norman's paradigm to the halogenated xanthenes.

For at least the above-stated reasons, Applicants respectfully submit that the combination of the references in improper and as a result, the rejection of Claim 14 under 35 U.S.C. 103(a) over Neckers in view of Norman is improper. Accordingly, it is respectfully requested that this rejection be withdrawn.

## VII. Claim Rejections - 35 USC §103 (Serafini, Neckers or Fondren)

The Examiner further rejects Claims 2 and 30 under 35 U.S.C. § 103(a) as being unpatentable over Serafini or Neckers or Fondren. This rejection is also respectfully traversed.

More specifically, the Examiner's stated basis for this rejection is an opinion that the only substantive difference between the claimed invention and the respective teachings in Serafini, Neckers or Fondren is the "effective variable" of concentration.[6] Applicants dispute this position for at least several reasons:

A. Serafini does not disclose a radiosensitizer medicament.

As discussed in detail *supra*, the composition in Serafini is a diagnostic agent, not a radiosensitizer pharmaceutical composition or medicament. Moreover, Serafini's diagnostic agent utilizes a radioactive form of Rose Bengal that is not the subject of the rejected claims of the present application. Further, it does not disclose the salt of the halogenated xanthene as recited in the claims.

Accordingly, the teachings in Serafini are not relevant to the patentability of the claimed concentrations of non-radioactive halogenated xanthenes in the present application.

B. Neckers does not disclose a radiosensitizer medicament.

As discussed *supra*, Neckers fails to teach or suggest a radiosensitizer pharmaceutical composition or medicament that contains Rose Bengal or any other halogenated xanthene. Accordingly, the teachings in Neckers are not relevant to the patentability of the claimed concentrations of halogenated xanthenes in the present invention.

C. Fondren does not disclose a radiosensitizer medicament.

As discussed *supra*, Fondren fails to teach or suggest a radiosensitizer pharmaceutical

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[6] This is the basis of record in the Office Action of September 23, 2003.

composition or medicament that contains Rose Bengal or any other halogenated xanthene. Fondren also fails to teach or suggest the radiosensitizer properties of the claimed pharmaceutical compositions or medicaments. Accordingly, the teachings in Fondren are not relevant to the patentability of the claimed concentrations of halogenated xanthenes in the present invention.

In conclusion, the teachings in Serafini, Neckers, or Fondren, taken alone or in any hypothetical combination, fail to disclose or suggest the claimed radiosensitizer pharmaceutical composition or medicament containing Rose Bengal or any other halogenated xanthene. Since they fail to disclose the subject matter of independent Claims 1 and 29, they can have no relevance to the claimed "effective variables" enumerated in Claims 2 and 30 dependent thereupon. Accordingly, Applicants respectfully request that this rejection be withdrawn.

## VIII. Claim Rejections - 35 USC §103 (in view of Khaw)

The Examiner also rejects Claims 6, 13, 21, 34, 40 and 49 under 35 U.S.C. §103(a) as being unpatentable over Serafini or Neckers or Fondren in view of Khaw. In order to advance the prosecution of this application, Claims 6 and 34 have been canceled by Applicants, rendering the rejection of these claims moot. The rejection of the remaining enumerated claims is respectfully traversed.

The Examiner's stated basis for this rejection appears to be an opinion that Khaw teaches: (a) certain forms of targeting based on immunoliposomes (see p. 11-12 of the Final Rejection); and (b) use of certain gamma imaging methods (see p. 12 of the Final Rejection). Applicants dispute the relevance of both alleged features for at least several reasons:

A. Liposomal targeting by Khaw is unrelated to the amended claims.

Applicants have canceled Claims 6 and 34, and excluded antibodies targeting from amended independent Claims 1 (base claim for rejected Claim 13), 16 (base claim for rejected Claim 21), 29 (base claim for rejected Claim 34 and 40), and 47 (base claim for rejected Claim 49).[7] It is believed that these amendments, which exclude any superficial similarity to the teachings of Khaw, address the Examiner's first basis for rejection of the enumerated claims. In particular, the amended claims specially recite that the claimed halogenated xanthenes are sodium or potassium salts of a halogenated xanthene. Such salts exclude the immunoconjugates taught by Khaw, thereby rendering Khaw irrelevant.

B. Khaw teaches use of gamma-emission imaging for diagnostics whereas the present invention concerns therapeutic treatment with applied gamma radiation.

As described in detail in Applicants' Amendment B in response to the Office Action of September 23, 2003, the teachings in Khaw are limited to use of gamma radiation in a diagnostic mode. To achieve this objective, Khaw teaches attachment of gamma-emitting radionuclides to diagnostic agents and subsequent imaging of their distribution in the body via detection of gamma emissions from such radiolabeled diagnostic agents.

In contrast, amended independent Claims 1 (base claim for rejected Claim 13), 16 (base claim for rejected Claim 21), 29 (base claim for rejected Claim 34 and 40), and 47 (base claim for rejected Claim 49) are directed to non-radioactive pharmaceutical compositions which, by definition, do not

[7] These amendments were performed in the spirit of advancing the prosecution of this application and are not believed to be Festo-type amendments.

contain gamma-emitting radionuclides.[8] It is believed that these amendments, which further exclude any superficial similarity to the teachings of Khaw, address the Examiner's second basis for rejection of the enumerated claims. In particular, the amended claims specifically recite that the claimed halogenated xanthenes do not contain a radioisotope (and hence contain no gamma-emitting radionuclides). Such compositions exclude the gamma-emitting substances taught in Khaw. Accordingly, Khaw has no relevance to the claimed invention.

C. Serafini, Neckers and Fondren have no bearing to the claimed invention; and combining these with Khaw fails to yield the claimed invention.

As discussed *supra*, neither Serafini, nor Neckers, nor Fondren disclose nor suggest the claimed radiosensitizers pharmaceutical compositions or medicaments that contain Rose Bengal or any other halogenated xanthene. Combination of these teachings with those in Khaw (even if such combination were proper) fails to redress this shortcoming since none of these references suggest a therapeutic agent consisting of any halogenated xanthene that becomes therapeutically active in the body upon irradiation with ionizing radiation. Accordingly, alone or in any combination, these references would not have rendered the claimed invention obvious.

Therefore, for at least the aforementioned reasons, Applicants respectfully submit that the combination of these references is improper and even if combined, fail to disclose or suggest the claimed invention. Hence, the claims are patentable over the cited references, and it is respectfully requested that this rejection be withdrawn.

## IX. Examiner's Response to Prior Arguments

In preparing this Amendment, Applicants have carefully considered the detailed response of

[8]Applicants note that the specific amendments responsible for this exclusion were performed in the spirit of advancing the prosecution of this application and are not believed to be Festo-type amendments.

the Examiner to Applicants' prior arguments filed on March 12, 2004. Applicants believe that the claim amendments and supporting arguments contained in the current response address the issues raised by the Examiner. Specifically, the current claim amendments make it clear that the claimed subject matter is not Rose Bengal or any other halogenated xanthene, but rather specific medicinal agents that contain a sodium or potassium salt of a halogenated xanthene, provided that the halogenated xanthene does not contain a radioisotope. Applicants further submit that such agents are patentably distinct from the cited references, and merit protection under U.S. Letters Patent.

## X. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this Amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

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